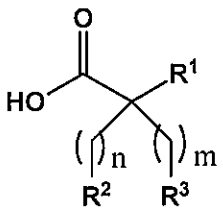
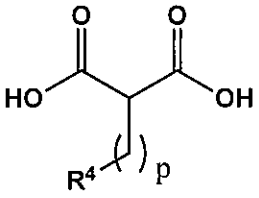
CLAIMS

1. A conjugate comprising a biomolecule linked to a fatty acid via a linker wherein the fatty acid has the following Formulae A1 or A2:



A1



A2

R^1 is CO_2H or H;

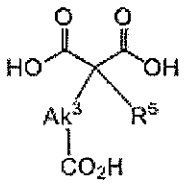
R^2, R^3 and R^4 are independently of each other H, OH, CO_2H, -CH=CH_2 or –C≡CH;

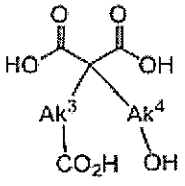
n, m and p are independently of each other an integer between 6 and 30;

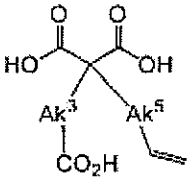
wherein the biomolecule prior to coupling with the linker has an amino functional group, and wherein the linker prior to incorporation into the conjugate, contains a terminal azido, a terminal carboxylic acid, or a terminal protected glutamic acid at one end and a terminal amino group at the other end,

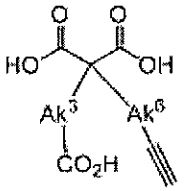
or an amide, ester or pharmaceutically acceptable salt thereof.

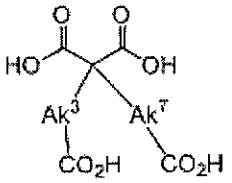
2. A conjugate according to claim 1 wherein the fatty acid is selected from



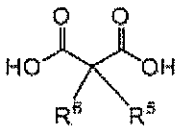






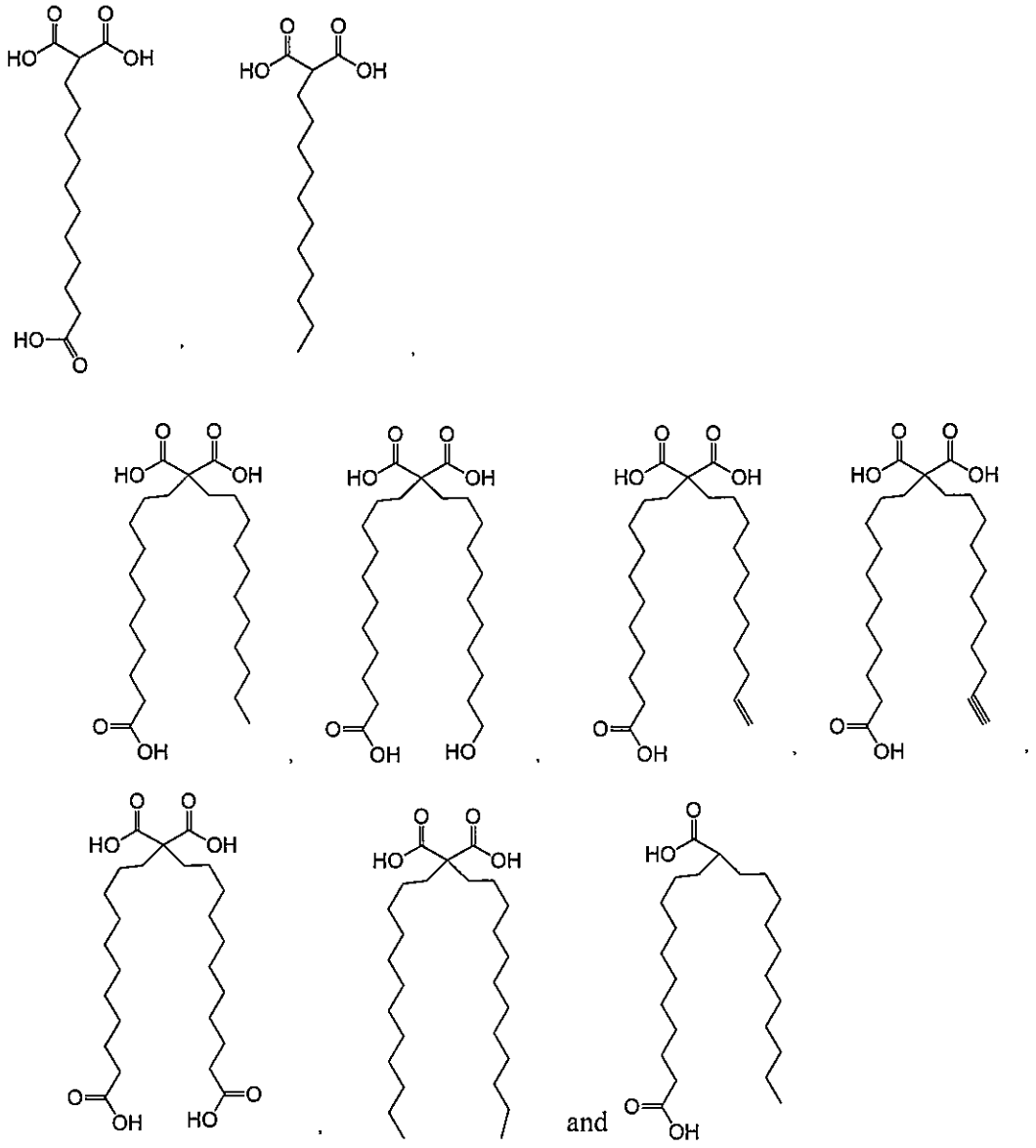


and



wherein Ak^3, Ak^4, Ak^5, Ak^6 and Ak^7 are independently a linear (C_{8-20})alkylene, R^5 and R^6 are independently linear (C_{8-20})alkyl, or an amide, an ester or a pharmaceutically acceptable salt thereof.

3. A conjugate according to claim 1 wherein the fatty acid is selected from:

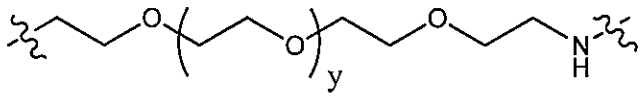


or an amide, ester or a pharmaceutically acceptable salt thereof.

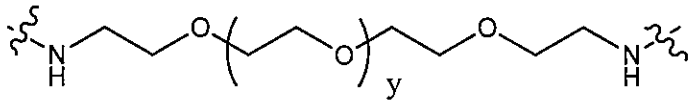
4. A conjugate according to claim 1, 2 or 3 wherein the linker comprises alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, polyethylene glycol, one or more natural or unatural

amino acids, or combination thereof, wherein each of the alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, polyethylene glycol and/or the natural or unatural amino acids are optionally combined and linked together or linked to the biomolecule and/or to the fatty acid moiety via a chemical group selected from –C(O)O-, -OC(O)-, -NHC(O)-, -C(O)NH-, -O-, -NH-, -S-, -C(O)-, -OC(O)NH-, -NHC(O)-O-, =NH-O-, =NH-NH- or =NH-N(alkyl)-; or an amide, ester or a pharmaceutically acceptable salt thereof.

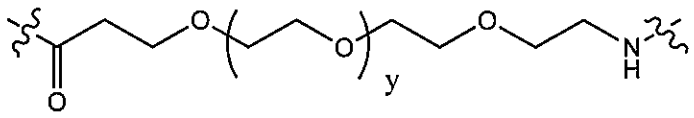
5. A conjugate according to any one of claims 1 to 4 wherein the linker comprises an unbranched oligo ethylene glycol moiety of Formula:



,

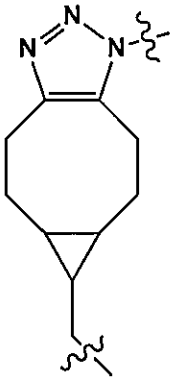
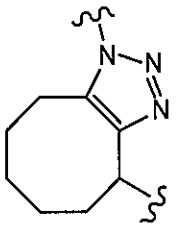
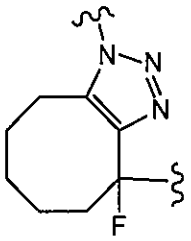
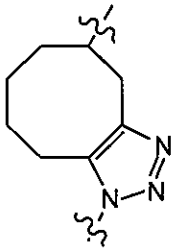
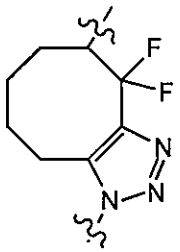
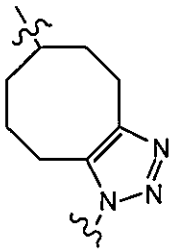
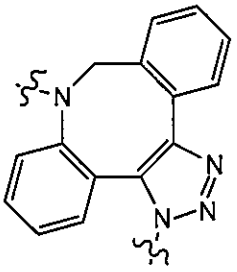
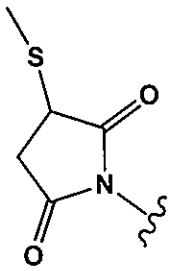
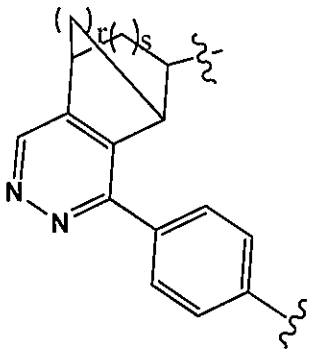


or,



wherein y is 0 to 34 ;or an amide, an ester or a pharmaceutically acceptable salt thereof.

6. A conjugate according to any one of claims 1 to 5 wherein the linker comprises a heterocyclic moiety of the following Formula:


,

,

,

,

,

,

,

,

, and

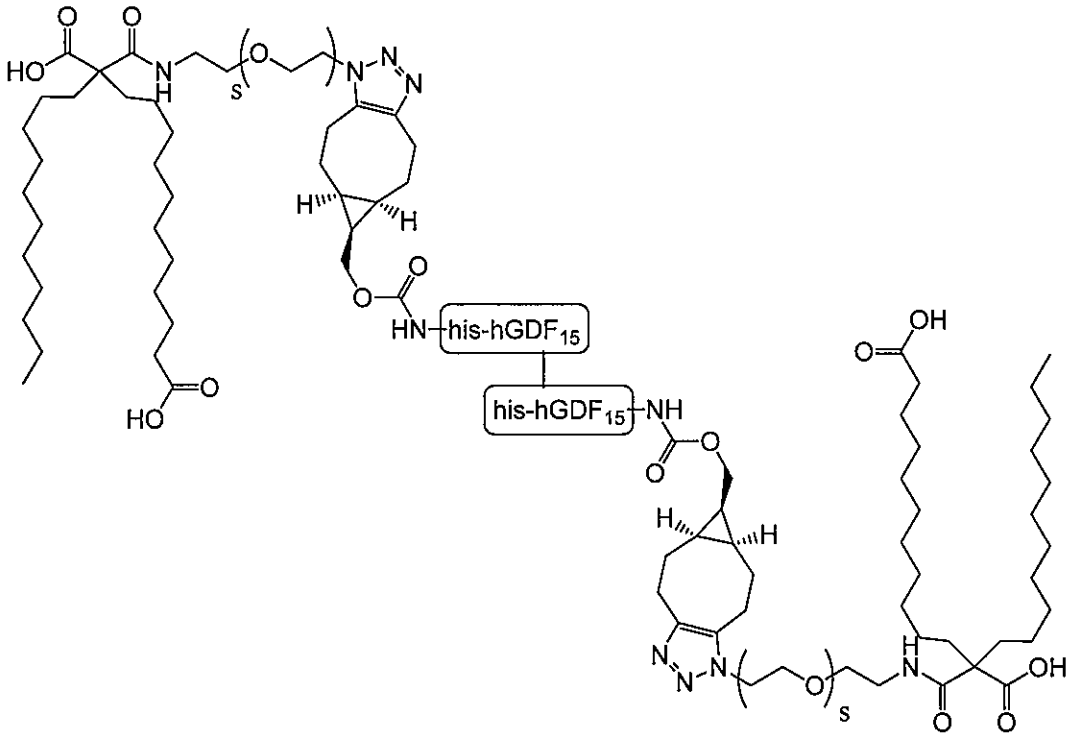
wherein r is an integer of 0 to 2 and s is an integer of 0 to 3; or an amide, an ester or a pharmaceutically acceptable salt thereof.

7. A conjugate according to any one of the preceding claims wherein the linker comprises one or more amino acids independently selected from histidine, methionine, alanine, glutamine, asparagine and glycine; or an amide, an ester or a pharmaceutically acceptable salt thereof.

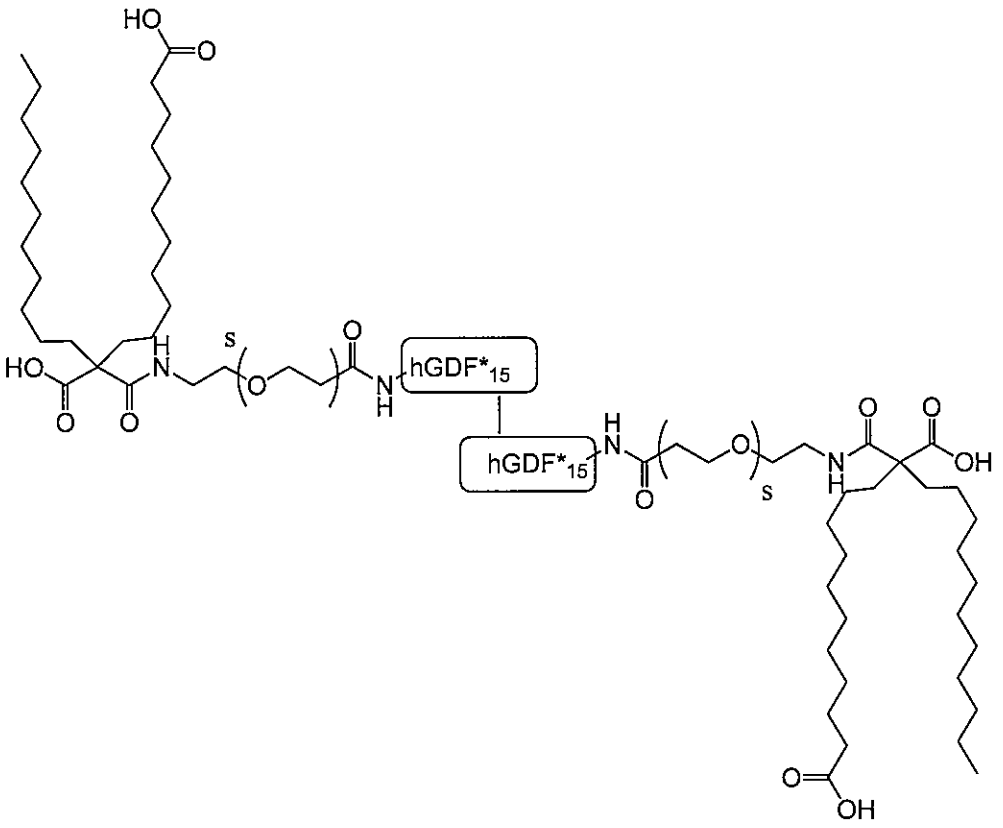
8. A conjugate according to any one of the preceding claims wherein the biomolecule is selected from: 1) human Growth Differentiation Factor 15 (GDF15), homologs, mutants or a

dimer thereof; 2) an APJ agonist peptide, 3) oxytocin receptor agonist peptide, 4)serelaxin, 5)NPFF, 6) a PIP peptide, 7)an FGF23 peptide 8) AgRP peptide and 9) a siRNA; or an amide, an ester or a pharmaceutically acceptable salt thereof.

9. A conjugate according to claim 1 or 2 wherein the biomolecule linked to the fatty acid via a linker has one of the following Formulae:

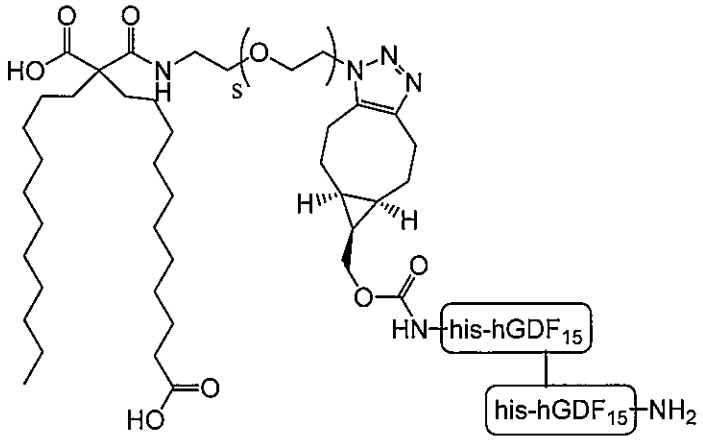


FORMULA C;



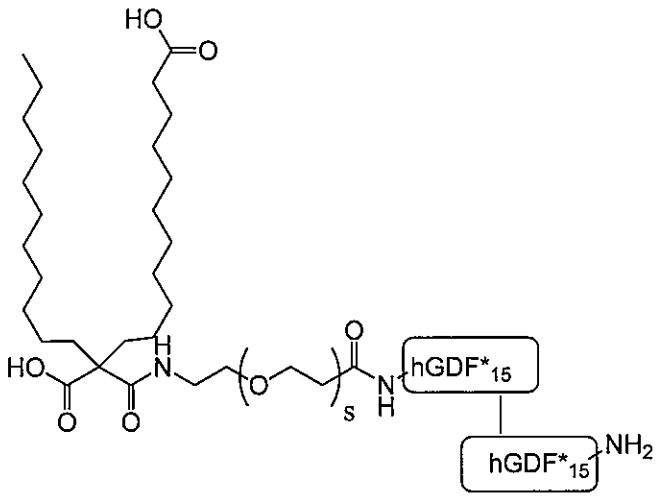
FORMULA D;

wherein in Formulae C and D; both monomeric units of his-hGDF15 or of hGDF15*are linked to the fatty acid moiety via a linker at both N-terminus; or



;

FORMULA E;



FORMULA F;

wherein in Formulae E and F, only one of the monomeric unit of his-hGDF15 or of hGDF15* is linked to the fatty acid moiety via a linker at the N-terminus; and

wherein hGDF15* is hGDF15 wherein the 2 or 3 amino acids at the N-terminus have been replaced with an amino acid sequence XH- or XHX'- respectively,

wherein H is histidine and X and X' are independently selected from M and A; and

wherein his-hGDF15 is hGDF15 wherein a tag, comprising 1 to 6 histidine amino acids and optionally 1 or 2 methionine amino acids, has been added to the N-terminus of hGDF15; and s is an integer between 20-30; and

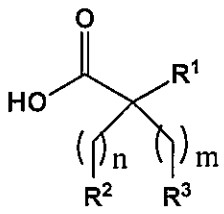
wherein the line between the 2 monomeric units of his-hDGF15 or the 2 monomeric units of hGDF15* represent a disulfide bond.

10. A mixture comprising the conjugate according to claim 9 having Formula C and the conjugate according to claim 9 having Formula E or a mixture comprising the conjugate according to claim 9 having Formula D and the conjugate according to claim 9 having Formula F.

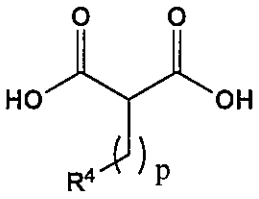
11. A conjugate according to any one of the preceding claims wherein the biomolecule is MH(199-308)hGDF15, MHA(200-308)hGDF15, AHA(200-308)hGDF15 or AH(199-308)GDF15; or a dimer thereof.

12. A conjugate comprising a biomolecule linked to a fatty acid via a linker

wherein the fatty acid has the following Formulae A1 or A2:



A1



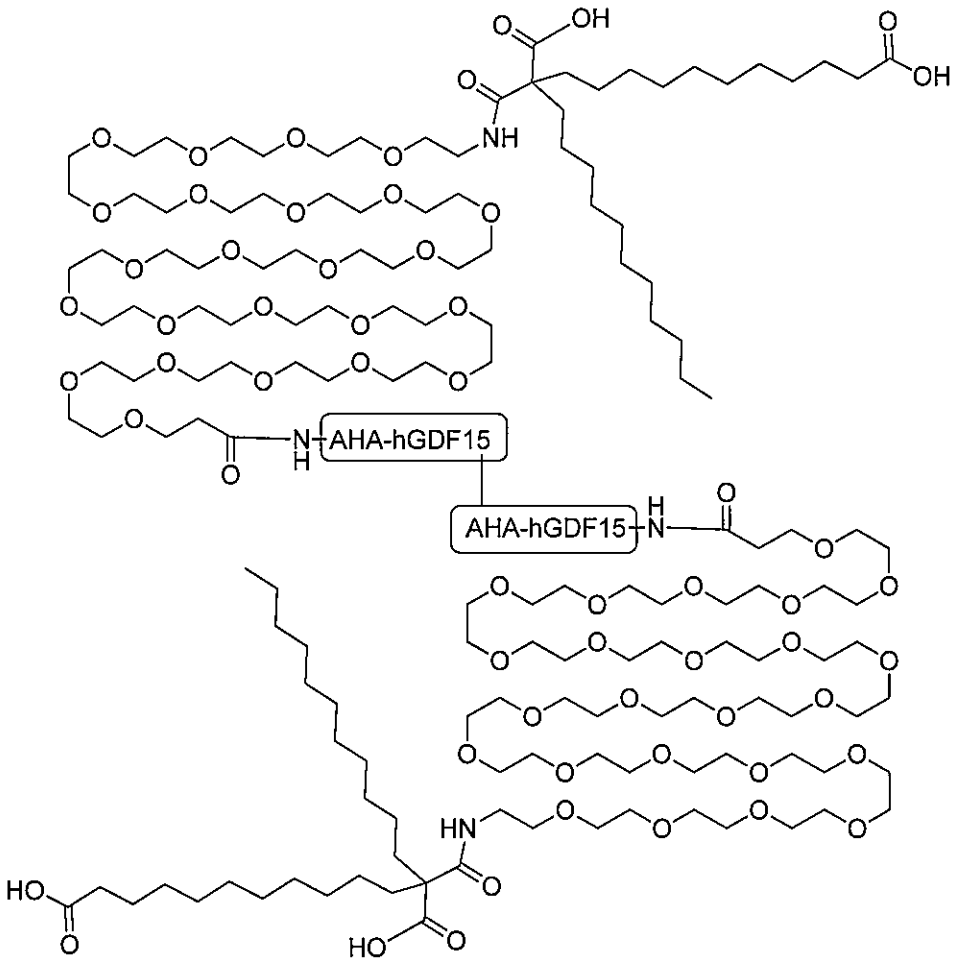
A2

R^1 is CO_2H or H;

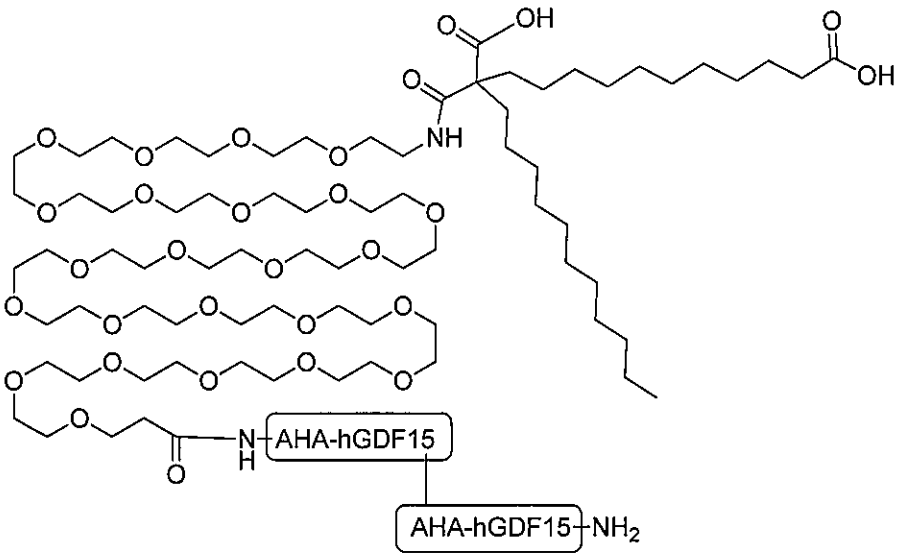
R^2, R^3 and R^4 are independently of each other H, OH, CO_2H, $-CH=CH_2$ or $-C\equiv CH$;

n, m and p are independently of each other an integer between 6 and 30;

wherein the biomolecule prior to coupling with the linker has an amino functional group, and wherein the linker prior to incorporation into the conjugate, contains a terminal azido, a terminal carboxylic acid, or a terminal protected glutamic acid at one end and a terminal amino group at the other end, wherein the biomolecule linked to a fatty acid via a linker is of Formula G or of Formula H:



Formula G;



FORMULA H.

wherein AHA-hGDF15 is SEQ ID NO: 7 and the fatty acid is linked via a linker at the N-terminus of one or of two monomeric units and wherein the line between the two AHA-hGDF15 units represent a disulfide bond.

13. A mixture comprising the conjugate according to claim 12 having Formula G and the conjugate according to claim 12 having Formula H.

14. A mixture according to claim 13, wherein the mixture is a 1:1 molar ratio of a conjugate of Formulae G and a conjugate of Formula H.

15. A conjugate according to any one of preceding claims wherein the fatty acid moiety is attached the N-terminus of the peptide or protein via a linker; or an amide, an ester or a pharmaceutically acceptable salt thereof.

16. A conjugate according to any one of the preceding claims wherein the conjugate has a plasma stability half-life of more than 10h, more than 20h or more than 30h.

17. A conjugate according to any one of the preceding claims where the improvement of plasma stability compared to the non-conjugated biomolecule is 2 fold, 5 fold, 10 fold, 20 fold, 30 fold, 40 fold, 50 fold or 75 fold.

18. A conjugate according to any one of claims 1 to 9, 11, 12 and 15-17, or a mixture of conjugates according to claim 10, 13 or 14, or an amide, an ester or a pharmaceutically acceptable salt thereof, for use as a medicament.

19. A conjugate according to any one of claims 1 to 9, 11, 12 and 15-17, or a mixture of conjugates according to claim 10, 13 or 14, or an amide, an ester of a pharmaceutically acceptable salt thereof, wherein the biomolecule is human Growth Differentiation Factor 15 (GDF15), homologs, variants, mutants, fragments and other modified forms thereof, for use in the treatment or prevention of metabolic disorders or diseases, diabetes, type 2 diabetes mellitus, obesity, pancreatitis, dyslipidemia, alcoholic and nonalcoholic fatty liver disease/steatohepatitis and other progressive liver diseases, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, metabolic syndrome, hypertension, cardiovascular disease, atherosclerosis, peripheral arterial disease, stroke, heart failure, coronary heart disease, diabetic complications (including but not limited to chronic kidney disease), neuropathy, gastroparesis and other metabolic disorders.

20. A Combination comprising a therapeutically effective amount of a conjugate according to any one of claims 1 to 9, 11, 12 and 15-17, or a mixture of conjugates according to claim 10, 13 or 14, or an amide, an ester or a pharmaceutically acceptable salt thereof, wherein the biomolecule is human Growth Differentiation Factor 15 (GDF15), homologs and mutants thereof; and one or more therapeutically active co-agent.

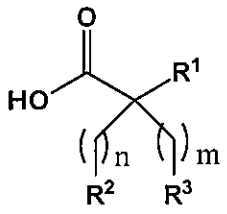
21. A combination according to claim 20 wherein the co-agent is selected from antidiabetic agent, hypolipidemic agent, anti-obesity agents, anti-hypertensive agents, and agonists of peroxisome proliferator-activator receptors.

22. A combination according to claim 21 wherein the co-agent is selected from insulin, insulin derivatives and mimetics; insulin secretagogues; glyburide, Amaryl; insulinotropic sulfonylurea receptor ligands; thiazolidinediones, pioglitazone, balaglitazone, rivoglitazone, netoglitazone, troglitazone, englitazone, ciglitazone, adaglitazone, darglitazone, Cholesteryl ester transfer protein (CETP) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors; RXR ligands; sodium-dependent glucose cotransporter inhibitors; glycogen phosphorylase A

inhibitors; biguanides; alpha-glucosidase inhibitors, GLP-1 (glucagon like peptide-1), GLP-1 analogs, GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors, 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors; squalene synthase inhibitors; FXR (farnesoid X receptor), LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid, aspirin; orlistat or rimonabant; loop diuretics, furosemide, torsemide; angiotensin converting enzyme (ACE) inhibitors; inhibitors of the Na-K-ATPase membrane pump; neutralendopeptidase (NEP) inhibitors; ACE/NEP inhibitors; angiotensin II antagonists; renin inhibitors; β-adrenergic receptor blockers; inotropic agents, dobutamine, milrinone; calcium channel blockers; aldosterone receptor antagonists; aldosterone synthase inhibitors; fenofibrate, pioglitazone, rosiglitazone, tesaglitazar, BMS-298585 and L-796449.

23. A pharmaceutical composition comprising a therapeutically effective amount of a conjugate according to any one of claims 1 to 9, 11, 12 and 15-17; or a mixture of conjugates according to claim 10, 13 or 14, or an amide, an ester or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

24. A compound of Formula:



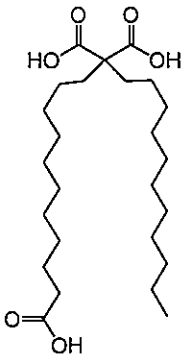
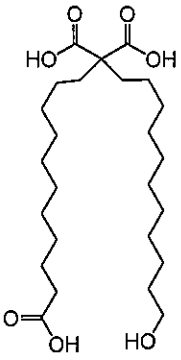
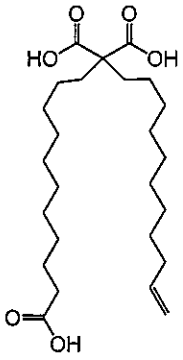
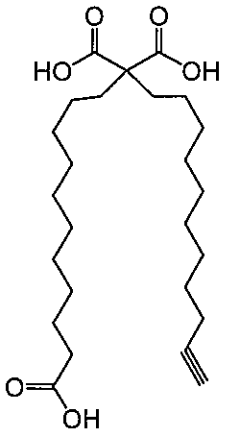
A1

R^1 is CO_2H;

R^2 and R^3 are independently of each other H, OH, CO_2H, $-CH=CH_2$ or $-C\equiv CH$; with the proviso that R^2 and R^3 are not identical;

n and m are independently of each other an integer between 6 and 30; or an amide, ester or pharmaceutically acceptable salt thereof.

25. A compound according to claim 24 selected from the group consisting of:




and